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SHORT REPORT



Severe chronic spontaneous urticaria in children – treatment options according to the guidelines and beyond – a 10 years review

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ABSTRACT

This is a retrospective study of 18 children with chronic spontaneous urticaria (CSU), where standard therapies, including up-dosing of antihistamines and omalizumab, were unable to cure the disease and where alternative strategies with experimental and off-label medication had to be used.

Materials: Being aware that our questionnaire is validated only for elder children or adults, we utilized the UAS7 to monitor disease control with the help of the parents.

Results: The UAS7 score decreased from a mean of 25 to an average of 13 after 8 weeks of therapy in 13 patients. Five patients had no significant reduction of UAS7 by week 8. In two of five patients, where periodic improvement was seen, omalizumab therapy was continued and showed complete response after 1–2 years. In three children, alternative treatments with cyclosporine and dupilumab, approved by the ethics committee, showed symptom improvement from a mean UAS7 of 29 to a mean value of 6.

Conclusions: When omalizumab therapy including up-dosing strategies or shortened interval shows no symptom improvement, alternative therapies, sometimes off-label have to be considered in time.

Abbreviations: CSU: chronic spontaneous urticaria; UAS7: Urticaria Activity Score 7 (days); CsA: cyclosporine; MCID: minimal clinically important difference

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Urticaria; children; omalizumab; dupilumab; autoimmunity

1. Introduction

According to the international guidelines, chronic urticaria (CU) is a common skin disease in adults and children. Autoimmune pathways are being discussed. Overall, triggers and causes like infection, medication, autoimmune disease and rare food allergens should be ruled out when therapy is unsuccessful. Prevalence of CU among children, although rare compared to adults, remains a therapeutic challenge. In most cases, an external cause cannot be identified (1).

The international guideline recommends that the disease has to be treated immediately while looking for possible causes and triggers. The first-line treatment for chronic spontaneous urticaria (CSU) is second-generation antihistamines and if not effective, dosage should be increased up to fourfold. Safety data are available for children and adults (2,3). If antihistamine therapy fails, omalizumab, a recombinant humanized monoclonal antibody, is an effective and safe second-line option (2). It was first approved in 2014 for treatment of urticaria in patients 12 years and older, but has been in clinical trials and is meanwhile approved for asthmatic children (from the age of 6) (4). The exact mechanism of action of omalizumab is still a matter of debate (5).

Like in adults, not all patients respond sufficient to those treatment options. Five out of 18 children in the age of 6–17 years showed no initial improvement to omalizumab. Off-label therapy was applied due to severity of symptoms and after

approval of the ethics committee. All children were non-responders to different first-line second generation antihistamines (including up-dosing therapeutic strategies) and received blood testing including measurements of IgE levels before starting omalizumab therapy.

2. Materials and methods

The UAS7 Questionnaire is a disease specific tool to assess disease activity in urticaria patients. It can be used to measure treatment response (6). The advantage of this tool is, that the disease activity is registered every day, so that the therapy response and the duration of the response can be monitored.

The urticaria activity was measured with the help of the parents using the UAS7 before start of omalizumab and at every consecutive visit (every 4 weeks).

An UAS7 of 0 was rated as symptom free, an UAS7 of 0–6 as well-controlled. The minimal clinically important difference (MCID) in the UAS7 score was rated in accordance to literature with a reduction of 9.5–10.5 points (6).

3. Results

Eighteen children suffered from CSU, all children were unsuccessfully treated with one or more second generation antihistamines including up-dosing until fourfold approved dosage (weight-adapted) before starting omalizumab. Five children

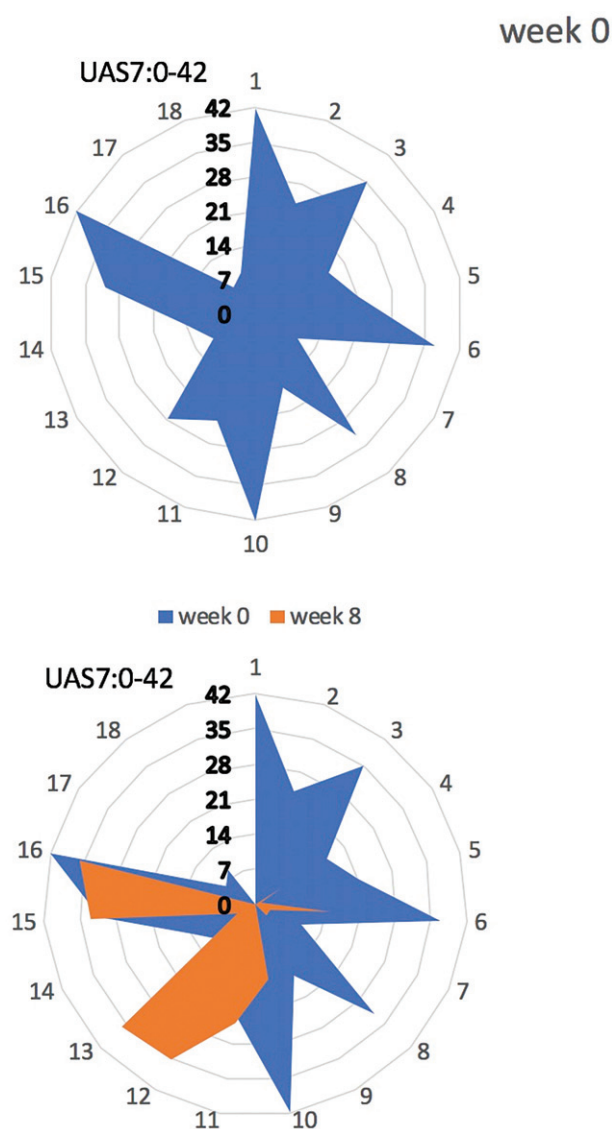


Figure 1. The UAS7 score (0–42) of children before treatment in week 0 (dark grey) and after initiation of omalizumab in week 8 (light grey). Patients 11, 12, 13, 15, and 16 with no or only slight improvement after initial treatment.

were under the age of 12. On average, UAS7 scores decreased from 24.6 (range 7–42) before therapy to 10.4 (range 0–36) after 8 weeks in 13 of 18 successfully treated children (Figure 1) (online resource Table 1).

In five of these 18 children, omalizumab response was delayed for more than 12 months or off-label alternatives had to be administered in order to achieve symptom control (online resource Table 2).

All off-label use was indicated due to the severity of symptoms, and approved by the ethics committee. There were not any mentionable side effects in this cohort.

Five patients treated with omalizumab had no to minimal reduction of UAS7 after week 8 (UAS7 range: 24–36). In two of those five non/late-responders, who did not show satisfying disease control at first, we decided to continue treatment with omalizumab. The decision to continue treatment was based on intermittent improvement of the UAS7 score, according to the MCID. The two children reached stable disease control (UAS7 < 6) after 1 year (UAS7 = 4) and after 2 years (UAS7 = 0).

In all five children, additional blood testing for autoimmunity (thyroid autoantibodies and tryptase elevation) and an autologous skin serum test (ASST) were performed. The ASST showed no abnormality; however, thyroid antibodies were positive in one child. In three patients, omalizumab therapy failed, even after up-dosing (450 or 600 mg) and/or interval shortening and long-term treatment. They were treated with cyclosporine for 3 months with a dosage of 3–4 mg/kg bodyweight, which led to symptom relieve in one patient and was discontinued after 3 months of treatment with no relapse (7).

In the two remaining patients, who showed inadequate response to cyclosporine (3–4 mg/kg body weight), off-label treatment with dupilumab 300 mg (an anti-IL 4/IL-13 antibody), licensed in atopic dermatitis, was started as mentioned in literature (8). One non-responder, with very high levels of IgE (3528 kU/l) and atopic disease (Figure 2), did not show adequate treatment response to cyclosporine, but significant improvement of symptoms after 4 weeks of dupilumab (week 8: UAS7 = 0). The therapy decision was made based on the high IgE-level. The other patient showed only slight improvement under dupilumab treatment at first, but symptoms improved after 3 months of therapy.

4. Discussion

Due to the international urticaria guidelines, the gold standard treating urticaria in children, adolescents, and adults are second generation antihistamines up to a fourfold dosage (weight-adapted). If there is a lack of response, omalizumab is approved for CSU or CombU (12 years and older).

The highest evidence for treatment in CSU patients exists for omalizumab – mostly in adults and only in a small cohort for adolescents from the age of 12. If omalizumab fails, cyclosporine is an alternative treatment option even in children (9).

In our outpatient clinic, on average we see about 100 children with urticaria every year. Mostly, they respond well to first-line therapy including up-dosing second generation antihistamines to the fourfold licensed dosage (weight-adapted).

In two patients, late response to omalizumab was seen. This observation had been made previously and reported in adult studies (10). In general, if there was a partial response after 3–6 months, we continued treatment like other groups (11). A periodically increased dosage or a shortened interval was applied during the course of treatment, depending on occurrence of symptoms during or at the end of the treatment interval.

It is known, that patients with autoimmune disease show sometimes limited benefit from an omalizumab therapy (12,13). In our pediatric cohort, autoimmune thyroiditis was present in one out of three children non-respondent to omalizumab. Neither up-dosing, cycle-shortening strategies nor cyclosporine and substitution of thyroid hormones resolved the problem. It was the off-label use of dupilumab, an IL-4/IL-13 antagonist, which led to significant improvement and is currently in trial for treatment of CSU (8).

The reason for late response to omalizumab in two children, might have been a high IgE-level, although there are reports stating the opposite (14). Retrospectively, treatment with dupilumab might have resulted in earlier symptom control. In children with a high level of IgE, who show no improvement to omalizumab nor cyclosporine, dupilumab 200 mg or 300 mg

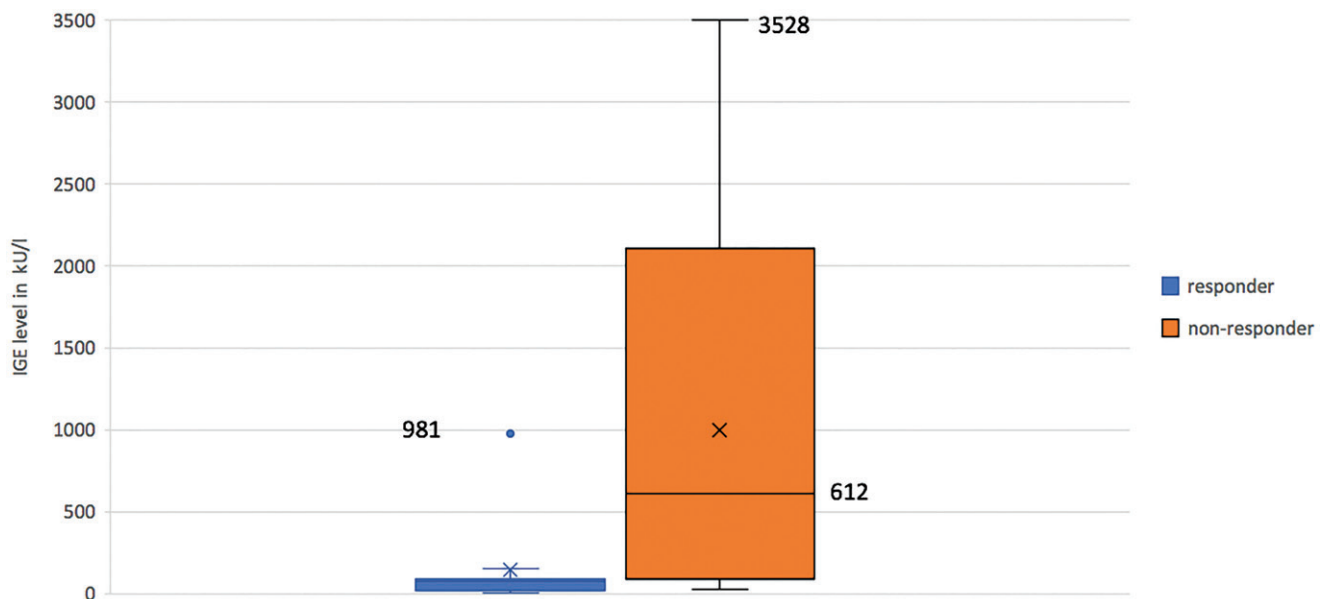


Figure 2. Levels of IgE (kU/l) in patients responding to omalizumab treatment (light Grey) and in the 5 non/late-responders (dark Grey) shown in boxplots.

weight-adapted every 2 weeks, may be an option. Moreover, cyclosporine is not recommended for long-term treatment.

Our experience shows, that for some, but not all patients with CSU, omalizumab is a safe and effective add-on treatment for a prolonged period of time. After increasing the dosage up to 450/600 mg in non-responders (weight-adapted) or shortening of the interval, alternative treatment protocols, even off-label, have to be kept in mind. In our case, this involved treatment with cyclosporine and/or dupilumab. Since 2019, new monoclonal antibodies such as ligelizumab are in trial for children age 12 and older (15), their efficacy has to be seen. Unfortunately, until today, no validated disease-specific scores are available to rate the burden of disease in children.

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Consent for publication

All authors carefully read the paper and gave their consent.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics declaration

This research is approved by the ethics commission of Rhineland-Palatinate, Germany.

Disclosure statement

Mann, Caroline: Novartis, Urticaria Network e.V. (UNEV); Sohn, Anna: Novartis; Lang, Berenice: Novartis; Zimmer, Sebastian:

Novartis; Peveling-Oberhag, Adriane: none; Staubach, Petra: Novartis, Pfizer, Sanofi, Hexal, Urticaria Network e.V. (UNEV).

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References

- Caffarelli C, Paravati F, El Hachem M, et al. Management of chronic urticaria in children: a clinical guideline. *Ital J Pediatr.* 2019;45(1):101.
- Wood RA, Khan DA, Lang DM, et al. American Academy of Allergy, Asthma and Immunology response to the EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of Urticaria 2017 revision. *Allergy.* 2019;74(2):411–413.
- Licari A, Marseglia A, Caimmi S, et al. Omalizumab in children. *Paediatr Drugs.* 2014;16(6):491–502.
- Efficacy and Safety of Omalizumab in Children (6–<12 years) with moderate-severe, inadequately controlled allergic asthma; 2004. Available from: <https://clinicaltrials.gov>
- Kaplan AP, Gimenez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. *Allergy.* 2017;72(4):519–533.
- Mathias SD, Crosby RD, Zazzali JL, et al. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol.* 2012;108(1):20–24.
- Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. *J Allergy Clin Immunol Pract.* 2019;7(5):1659–1661.e1.
- Neverman L, Weinberger M. Treatment of chronic urticaria in children with antihistamines and cyclosporine. *J Allergy Clin Immunol Pract.* 2014;2(4):434–438.

9. Vadasz Z, Tal Y, Rotem M, et al. Omalizumab for severe chronic spontaneous urticaria: real-life experiences of 280 patients. *J Allergy Clin Immunol Pract.* 2017;5(6): 1743–1745.
10. Ferrer M, Boccon-Gibod I, Goncalo M, et al. Expert opinion: defining response to omalizumab in patients with chronic spontaneous urticaria. *Eur J Dermatol.* 2017;27(5):455–463.
11. Kudryavtseva AV, Neskorođova KA, Staubach P. Urticaria in children and adolescents: an updated review of the pathogenesis and management. *Pediatr Allergy Immunol.* 2019; 30(1):17–24.
12. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy.* 2018; 73(7):1393–1414.
13. Halilovic E, Beslic N, Kurtovic N. Thyroid autoimmunity in patients with chronic urticaria. *Med Arch.* 2017;71(1): 29–31.
14. Ertas R, Ozyurt K, Atasoy M, et al. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. *Allergy.* 2018;73(3):705–712.
15. A phase III study of efficacy and safety of ligelizumab in the treatment of CSU in adolescents and adults inadequately controlled with H1-antihistamines; [Internet]. Available from: clinicaltrials.gov